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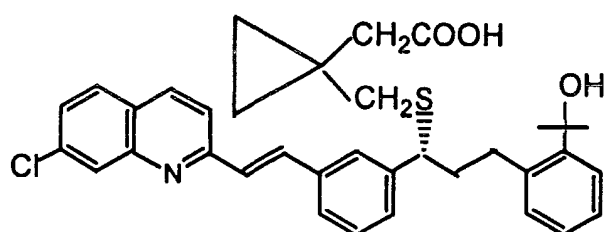
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(54) Title: NOVEL ANHYDROUS AMORPHOUS FORMS OF MONTELUKAST SODIUM SALT



(I)

(57) Abstract: The present invention relates to novel anhydrous amorphous forms of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinoliny] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts (Montelukast alkali salts) to processes for their preparation, to compositions containing them and to methods of treatment using the same. Montelukast is a leukotriene antagonist, is useful as anti-asthmatic, anti-allergic,

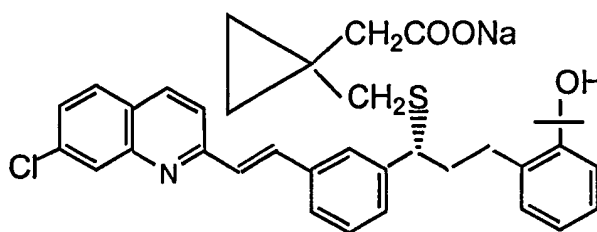
anti-inflammatory and cytoprotective agent. Montelukast is represented by the formula (I).

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## NOVEL ANHYDROUS AMORPHOUS FORMS OF MONTELUKAST SODIUM SALT

The present invention relates to novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts (Montelukast alkali salts) to processes for their preparation, to compositions containing them and to methods of treatment using the same.

Montelukast Sodium, chemically known as [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid (Montelukast) sodium salt is represented by the formula:



Montelukast sodium, a leukotriene antagonist, is useful as anti-asthmatic, anti-allergic, anti-inflammatory and cytoprotective agent and is hence useful in the treatment of angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis, and allograft rejection.

EP 480717 discloses certain substituted quinoline compounds including [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast sodium), and methods for their preparation.

The reported synthesis of Montelukast Sodium proceeds through corresponding methyl ester and involves coupling methyl 1-(mercaptomethyl) cyclopropaneacetate with a mesylate generated *in situ*. The methyl ester of Montelukast free acid is hydrolyzed to the free acid and the latter converted directly to the corresponding sodium salt. This process is not particularly suitable for large-scale production because it requires tedious chromatographic purification of the methyl ester intermediate and/or the final product, and the product yields are low.

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WO Patent Application 95/18107 discloses an improved process for the preparation of crystalline Montelukast sodium salt, which comprises the generation of dilithium dianion of 1-(mercaptomethyl) cyclopropaneacetic acid followed by condensation with 2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl) ethenyl) phenyl)-3-methanesulfonyloxypropyl) phenyl)-2-propanol to afford the Montelukast acid which is then converted, via dicyclohexyl amine salt, to its corresponding sodium salt. The obtained sodium salt is further crystallized from a mixture of toluene: acetonitrile to obtain crystalline Montelukast sodium.

The PCT application further designates the products obtained as per EP 480717 as amorphous sodium salts, which are hydrated and often not ideal for pharmaceutical formulation.

It has been disclosed earlier that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to crystalline forms [Konne T., Chem pharm Bull., 38, 2003(1990)]. For some therapeutic indications one bioavailability pattern may be favoured over another. An amorphous form of Cefuroxime axetil is a good example for exhibiting higher bioavailability than the crystalline form.

Since Montelukast sodium is useful as anti-asthmatic, anti-allergic, anti-inflammatory and cytoprotective agent and amorphous forms of a number of drugs have been disclosed to exhibit different dissolution characteristics and in some cases different bioavailability patterns when compared to crystalline forms, the present invention, hence, aims to provide novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts and to processes for the preparation thereof.

The present invention also provides pharmaceutical compositions and pharmaceutical methods of treatment using novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts.

Another embodiment of the present invention is to provide methods for the preparation of the anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts (Montelukast alkali salts) which comprises dissolution of

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Montelukast free acid in aromatic hydrocarbon solvent or halogenated solvent and converting the free acid to its alkali salt, accompanied by addition of a cyclic or acyclic hydrocarbon solvent or mixtures thereof, followed by isolation of the desired compound.

Still another embodiment of the present invention is to provide pharmaceutical formulations containing an anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt.

An additional embodiment of the present invention is to provide pharmaceutical methods of treatment using anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts.

#### Brief Description Of The Accompanying Drawing

Fig. 1 is X-ray powder diffractogram of novel anhydrous amorphous form of Montelukast Sodium.

The present invention provides novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts, preferably, anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt.

The present invention also provides a process for preparation of anhydrous amorphous forms of Montelukast alkali metal salts. The anhydrous amorphous forms of Montelukast alkali metal salts are prepared by dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon. The solution of free acid of Montelukast is converted into alkali salt by use of alkaline metal hydroxide or an alkaline metal alkoxide in the presence of C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol or by use of alcoholic alkaline metal hydroxide or an alcoholic metal alkoxide.

One process for preparing amorphous forms of Montelukast alkali metal salts comprises:

i) dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;

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ii) converting the dissolved acid of step i) to corresponding alkali salt using an alkaline metal hydroxide or an alkaline metal alkoxide in the presence of C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent; and

iv) isolating amorphous form of Montelukast alkali salt by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

According, to another embodiment, the present invention provides a process for preparation of amorphous forms of Montelukast alkali metal salts, which comprises:

i) dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide, followed by;

iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent; and

iv) isolating amorphous form of Montelukast alkali salt by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

The alkaline metal may be selected from calcium, sodium, potassium, or magnesium. Preferably, the alkaline metal is sodium.

According, to another embodiment, the present invention provides a process for preparation of novel anhydrous amorphous form of Montelukast Sodium, which comprises:

i) dissolving the free acid of Montelukast sodium in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding sodium salt using sodium hydroxide or sodium alkoxide in presence of C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent, and

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iv) isolating anhydrous amorphous form of Montelukast alkali salt sodium by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

According, to another embodiment, the present invention provides a process for preparation of novel anhydrous amorphous form of Montelukast Sodium, which comprises:

i) dissolving the free acid of Montelukast sodium in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding sodium salt using alcoholic sodium hydroxide or alcoholic sodium alkoxide in presence of C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent, and

iv) isolating anhydrous amorphous form of Montelukast alkali salt sodium by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

In a preferred embodiment of the invention, the ratio of Montelukast free acid to C<sub>1</sub>-C<sub>2</sub> halogenated solvent or C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent in step i) is 1:1.5 to 1:6 w/v.

In a preferred embodiment of the invention, the ratio of Montelukast acid to C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol is 1:2-3 w/v.

In a preferred embodiment of the invention, the molar ratio of Montelukast acid to alkali metal hydroxide or alkaline metal alkoxide is 1:0.98 – 1.02, preferably, 1:1. In a preferred embodiment of the invention, the ratio of Montelukast acid to alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:2-4 w/v wherein the ratio of Montelukast acid to alkaline metal in alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:0.98 – 1.02 w/v. In step iii), the ratio of the reaction mass to the solvent is 1:1.2 to 1:4 w/v.

In precipitation of Montelukast alkali salt in step iv) the ratio of C<sub>1</sub>-C<sub>2</sub> halogenated solvent or C<sub>7</sub>-C<sub>8</sub> aromatic solvent to the C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon is 1:5 to 1:13 v/v. The preferred ratio is 1:6.5 v/v. This ratio is based on the amount of the C<sub>1</sub>-C<sub>2</sub> halogenated solvent or C<sub>7</sub>-C<sub>8</sub> solvent added in step iii).

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The C<sub>1</sub>-C<sub>2</sub> halogenated solvent may be selected from chloroform, dichloromethane or dichloroethane, preferably dichloromethane. The C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent may be selected from toluene, ethyl benzene or xylene, preferably toluene.

5           The alkali used in step ii) may be selected from sodium hydroxide, sodium methoxide, sodium ethoxide, methanolic sodium hydroxide, ethanolic sodium hydroxide, methanolic sodium methoxide, ethanolic sodium methoxide, methanolic sodium ethoxide, ethanolic sodium ethoxide, calcium hydroxide, calcium methoxide, calcium ethoxide, methanolic calcium hydroxide, ethanolic calcium hydroxide, methanolic calcium methoxide, 10 ethanolic calcium methoxide, methanolic calcium ethoxide, ethanolic calcium ethoxide, potassium hydroxide, potassium methoxide, potassium ethoxide, methanolic potassium hydroxide, ethanolic potassium hydroxide, methanolic potassium methoxide, ethanolic potassium methoxide, methanolic potassium ethoxide, ethanolic potassium ethoxide, magnesium hydroxide, magnesium methoxide, magnesium ethoxide, methanolic magnesium 15 hydroxide, ethanolic magnesium hydroxide, methanolic magnesium methoxide, ethanolic magnesium methoxide, methanolic magnesium ethoxide, ethanolic magnesium ethoxide, preferably the alkali is sodium hydroxide.

          The C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol may be selected from methanol, ethanol, propanol, butanol, 2-propanol or tertiary butanol, preferably methanol. The C<sub>5</sub>-C<sub>7</sub> 20 acyclic solvent may be selected from pentane, hexane, n-hexane, n-heptane or n-octane, preferably hexane or n-heptane. The C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon solvent may be selected from cyclopentane, cyclohexane or cycloheptane, preferably cyclohexane.

          Novel anhydrous amorphous forms of Montelukast alkali salts may be characterized by the X-Ray powder diffraction pattern. The present invention provides 25 anhydrous amorphous form of Montelukast Sodium that is characterized by its X Ray powder diffraction, substantially in accordance with Figure 1. The X-Ray diffraction pattern of anhydrous amorphous form of Montelukast Sodium was measured on a Rigaku Dmax 2000 with Cu K alpha-1 ISOKV/34mA, Degrees scanned: 3-45 degrees. Scan speed 3 degree/min.

30           The compounds of this invention can be used to prevent the synthesis, the action or the release of SRS-A or leukotrienes.

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The ability of the compounds of the present invention to antagonize the actions of the leukotrienes makes them useful for preventing or reversing the symptoms induced by the leukotrienes in a mammal including a human subject. This antagonism of the actions of leukotrienes indicates that the compounds of this invention and pharmaceutical compositions thereof are useful to treat, prevent, or ameliorate in mammals and especially in humans: 1) pulmonary disorders including diseases such as asthma, chronic bronchitis, and related obstructive airway diseases, 2) allergies and allergic reactions such as allergic rhinitis, contact, allergic conjunctivitis, and the like, 3) inflammation such as arthritis or inflammatory bowel disease, 4) pain, 5) skin disorders such as psoriasis, atopic eczema, and the like, 6) conditions related to cardiovascular disorders such as angina, myocardial ischemia, hypertension, platelet aggregation and the like, 7) renal insufficiency arising from ischaemia induced by immunological or chemical (cyclosporin) etiology, 8) migraine or cluster headache, 9) ocular conditions including inflammatory diseases such as uveitis, 10) hepatitis resulting from chemical, immunological or infectious stimuli, 11) trauma or shock states such as burn injuries, endotoxemia and the like, 12) allograft rejection, 13) prevention of side effects associated with therapeutic administration of cytokines such as interleukin II and tumor necrosis factor, 14) chronic lung diseases such as cystic fibrosis, bronchitis and other small and large-airway diseases, 15) cholecystitis and 16) glomerular nephritis.

The compounds of the present invention may also be used to treat or prevent mammalian (especially, human) disease states such as erosive gastritis; erosive esophagitis; diarrhea; cerebral spasm; premature labor; spontaneous abortion, dysmenorrhea, ischemia, noxious agent-induced damage of necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatotoxic agents such as CCl<sub>4</sub> and D-galactosamine; ischaemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced renal failure. The compounds also exhibit cytoprotective action. (See EP 0480717).

The magnitude of prophylactic or therapeutic dose of a compound of this invention will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of this invention and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range for anti-asthmatic, anti-allergic or anti-inflammatory use and generally, uses other



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than cytoprotection, lie within the range of from 0.001 mg to 100 mg per kg body weight of a mammal, preferably 0.01 mg to 10 mg per kg, and most preferably 0.1 to 1 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

5           The pharmaceutical compositions of the present invention comprise an anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt, as an active ingredient and may also contain a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, solvent, binder, stabilizer and the like and  
10 optionally other ingredients used in pharmaceutical formulations. The compositions may also comprise one or more additional therapeutic agents. The compositions of this invention include compositions suitable for oral, rectal, topical, parenteral, ocular, pulmonary, or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. The  
15 compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of the pharmacy.

Dosage forms include tablets, troches, dragees, powders, syrups, patches, liposomes, injections, dispersions, suspensions, solutions, capsules, creams, ointments and aerosols. Compositions which provide from 0.1 to 10.0 mg of the active ingredient are  
20 preferred.

In general, an effective amount means that amount of a compound of this invention that will elicit the biological or medical response that is being sought. Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal,  
25 topical, parenteral, ocular, pulmonary and nasal administration, any be employed.

The Montelukast free acid used for the preparation of the novel anhydrous amorphous forms of Montelukast alkali salts is prepared as per processes known in the prior art.

The following examples illustrate the invention but do not construe to limit  
30 the same.

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**EXAMPLES****Reference Example****Preparation of Montelukast free acid**

Montelukast dicyclohexylamine salt (250.0 g, 0.326 moles) is suspended in  
5 dichloromethane (2.5 lit.), followed by addition of water (1.25 lit.), acetic acid (28 ml, 0.489  
moles). The mixture is stirred for 30 minutes at ambient temperature. The layers are  
separated and the aqueous layer extracted with dichloromethane (1 x 500ml and 1 x 125 ml).  
The combined organic layers are washed with water (4 x 1.25lit.) and the organic layer  
separated. The organic layer thus obtained is dried over anhydrous sodium sulfate. The  
10 reaction solution is decanted, solvent from the reaction solution distilled under vacuum at  
below 50°C to afford the Montelukast free acid as residual mass.

**Example 1**

Montelukast free acid (260 g.) is dissolved in toluene (500ml) and the solvent  
is completely distilled off under vacuum at below 50°C to afford the residue. The residue  
15 thus obtained is further dissolved in toluene (750ml) and 0.5M methanolic sodium hydroxide  
solution (665ml) added and the mixture stirred for 15-30 minutes. The solvent from the  
reaction mass is distilled off under reduced pressure at below 50°C, followed by addition of  
toluene (500 ml) and distilling off 10-30% (v/v) of the reaction volume under reduced  
pressure at below 50°C. The concentrated reaction solution is added to hexane (2.5lit.) under  
20 Nitrogen atmosphere for 15-30 minutes at ambient temperature and stirred for 1-2 hours.  
The desired isolated compound is filtered under Nitrogen atmosphere and washed with  
hexane (500 ml), further the compound is filtered under vacuum. The wet compound was  
dried under vacuum at 70-80°C for 6-7 hours to yield amorphous form of Montelukast  
sodium. (Weight: 188 g., 94.90%, HPLC purity: 99.40%).

**Example 2**

Montelukast free acid (approx 26 g) is dissolved in toluene (50ml) and the  
solvent is completely distilled off under vacuum at below 50°C to afford the residue. The  
residue thus obtained is further dissolved in toluene (75ml) and 0.5M methanolic sodium  
hydroxide solution (69 ml) is added and the mixture stirred for 15-30 minutes. The solvent  
30 from the reaction mass was distilled off under reduced pressure at below 50°C followed by  
addition of toluene (300 ml) and charcoal treatment. The solvent from the reaction solution is

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distilled off completely under reduced pressure at below 50°C. The residual mass is dissolved in toluene (40 ml) and solution added to n-heptane (250 ml) under Nitrogen atmosphere for 15-30 minutes at ambient temperature and stirred for 1-2 hours. The desired isolated compound is filtered under Nitrogen atmosphere and washed with n-heptane (50 ml),  
5 further the compound is filtered under vacuum and dried under vacuum at 70-80°C for 2-3 days to yield amorphous form of Montelukast sodium. (Weight: 18.0 g., 91.0%, HPLC purity: 99.40%)

### Example 3

Montelukast free acid (14 g.) is dissolved in toluene (20 ml) and distilled off  
10 the solvent completely under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (30ml) and 0.5M methanolic sodium hydroxide solution (27 ml) is added and reaction mass stirred for 15-30 minutes. The solvent from the reaction mass is distilled off under reduced pressure at below 50°C followed by addition of toluene (20 ml) and distilling the solvent to obtain 10-30% (v/v) of the reaction volume under  
15 reduced pressure at below 50°C. The concentrated reaction solution is added to cyclo hexane (100 ml.) under Nitrogen atmosphere for 15-30 minutes at ambient temperature and stirred for 1-2 hours. The desired isolated compound is filtered under Nitrogen atmosphere and washed with cyclo hexane (20 ml), further the compound is filtered under vacuum. The wet compound is dried under vacuum at 70-85°C for 2-3 days to yield amorphous form of  
20 Montelukast sodium. (Weight: 6.8 g., 85.0%, HPLC purity: 99.10%).

### Example 4

Montelukast free acid (0 g.) is dissolved in toluene (20ml) and the solvent is distilled off under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (30ml) and 0.5M methanolic sodium hydroxide solution (27 ml)  
25 is added and reaction mass is stirred for 15-30 minutes. The solvent is distilled off completely under reduced pressure at below 50°C.

To the residue, dichloro methane (15 ml) is added. The resulting solution is added to n-heptane (200 ml) under nitrogen atmosphere for 15-30 minutes at ambient temperature. The reaction mass is stirred for 1-2 hours. The compound thus obtained is  
30 filtered under nitrogen atmosphere and washed with n-heptane (40 ml). The wet compound

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was dried under vacuum at 70-80°C for 2-3 days to yield amorphous form of Montelukast sodium. (Weight: 6.3 g., 78.70%, HPLC purity: 99.10%).

Fig-1 is characteristic X-ray powder diffraction pattern of amorphous form of Montelukast Sodium Salt. Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

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## C L A I M S

1. Novel anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt (Montelukast alkali salt).
- 5 2. Novel anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast Sodium).
3. The amorphous form according to claim 2, characterized by an X-ray powder diffraction pattern substantially in accordance with Fig-1.
- 10 4. A process for the preparation of anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt (Montelukast alkali salt), which comprises the steps of:
  - i) dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent
  - 15 or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;
  - ii) converting the dissolved acid of step i) to corresponding alkali salt using an alkaline metal hydroxide or an alkaline metal alkoxide in presence of C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol, followed by;
  - iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated
  - 20 solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent, and isolating novel amorphous form of Montelukast alkali salt by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.
5. A process for the preparation of anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt (Montelukast alkali salt), which
- 25 comprises the steps of:
  - i) dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;
  - ii) converting the dissolved acid of step i) to corresponding alkali salt
  - 30 using an alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide, followed by;

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iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent, and

iv) isolating novel amorphous form of Montelukast alkali salt by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

5 6. A process for the preparation of anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinoliny] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast sodium salt), which comprises the steps of:

i) dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent  
10 or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an sodium hydroxide or an sodium alkoxide in presence of C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated  
15 solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent, and

iv) isolating novel amorphous form of Montelukast sodium salt by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

7. A process for preparation of novel amorphous form of Montelukast Sodium, which comprises the steps of:

i) dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent  
20 or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to the corresponding sodium salt using alcoholic sodium hydroxide or alcoholic sodium alkoxide, followed by;

iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated  
25 solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent, and

iv) isolating novel amorphous form of Montelukast sodium by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

8. The process according to claim 4 or 5 wherein the alkaline metal is sodium, calcium, magnesium or potassium.

30 9. The process according to claim 4, wherein the alkaline alkoxide is selected from sodium methoxide or sodium ethoxide.

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10. The process according to claim 6, wherein the sodium alkoxide is sodium methoxide or sodium ethoxide.
11. The process according to claim 4, wherein the alkaline hydroxide is sodium hydroxide.
- 5 12. The process according to any one of claims 4 to 7, wherein the ratio of the free acid of Montelukast to C<sub>1</sub>-C<sub>2</sub> halogenated solvent or C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent in step i) is 1:1.5 to 1:6 w/v.
13. The process according to claim 4 or 6, wherein the ratio of Montelukast to C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol is 1:2-3 w/v.
- 10 14. The process according to claim 4, wherein the molar ratio of Montelukast acid to alkaline metal hydroxide or alkaline metal alkoxide acid is 1:0.98 – 1.02.
15. The process according to claim 6, wherein the molar ratio of Montelukast acid to sodium hydroxide or sodium alkoxide is 1:0.98 – 1.02.
16. The process according to claim 5, wherein the molar ratio of Montelukast acid to alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:2-4 w/v.
- 15 17. The process according to claim 7, wherein the molar ratio of Montelukast acid to alcoholic sodium hydroxide or alcoholic sodium alkoxide is 1:2-4 w/v.
18. The process according to claim 5, wherein the molar ratio of Montelukast acid to alkali in alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:
- 20 0.98 – 1.02 w/v.
19. The process according to claim 7, wherein the molar ratio of Montelukast acid to sodium in alcoholic sodium hydroxide or alcoholic sodium alkoxide is 1: 0.98 – 1.02 w/v.
20. The process according to any one of claims 4 to 7, wherein in step iii), the
- 25 ratio of the reaction mass to the solvent is 1:1.2 to 1:4 w/v.
21. The process according to any one of claims 4 to 7, wherein in step iv) the ratio of C<sub>1</sub>-C<sub>2</sub> halogenated solvent or C<sub>7</sub>-C<sub>8</sub> aromatic solvent to the C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon is 1:5 to 1:13 v/v.
22. The process according to any one of claims 4 to 7, wherein the C<sub>1</sub>-C<sub>2</sub>
- 30 halogenated solvent is selected from chloroform, dichloromethane or dichloroethane.

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23. The process according to claim 21, wherein the halogenated solvent is dichloromethane.
24. The process according to any one of claims 4 to 7, wherein the C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent is selected from toluene, ethyl benzene or xylene.
- 5 25. The process according to claim 24, wherein the aromatic hydrocarbon solvent is toluene.
26. The process according to any one of claims 4 or 6, wherein the C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol is selected from methanol, ethanol, propanol, butanol, 2-propanol or tertiary butanol.
- 10 27. The process according to claim 26, wherein the C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol is methanol.
28. The process according to any one of claims 4 to 7, wherein the C<sub>5</sub>-C<sub>7</sub> cyclic hydrocarbon solvent is selected from cyclopentane, cyclohexane or cycloheptane.
29. The process according to claim 27, wherein the cyclic hydrocarbon solvent is  
15 cyclohexane.
30. The process according to any one of claims 4 to 7, wherein the C<sub>5</sub>-C<sub>8</sub> acyclic hydrocarbon solvent is selected from pentane, hexane, n-hexane, n-heptane or n-octane.
31. The process according to claim 29, wherein the acyclic hydrocarbon solvent is hexane or n-heptane.
- 20 32. A composition comprising an effective amount of a compound of any one of claims 1-3 and a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, solvent, binder or stabilizer.
33. The composition according to claim 31, in the form of a tablet, troche, dragee, powder, syrup, patch, liposome, injection, dispersion, suspension, solutions, capsule, cream,  
25 ointment or aerosol.
34. The use of a compound of any one of claims 1-3, for the manufacture of a medicament, for preventing the synthesis, the action, or the release of SRS-A or leukotrienes.
35. The use of a compound of any one of claims 1-3, for the manufacture of a medicament for treating asthma.
- 30 36. The use of a compound of any one of claims 1-3, for the manufacture of a medicament for treating inflammatory diseases of the eye.



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37. The use of a compound of any one of claims 1 to 3, for preparing a medicament for treating, preventing or ameliorating 1) pulmonary disorders including diseases such as asthma, chronic bronchitis, and related obstructive airway diseases, 2) allergies or allergic reactions such as allergic rhinitis, contact dermatitis, or allergic conjunctivitis, 3) inflammation such as arthritis or inflammatory bowel disease, 4) pain, 5) skin disorders such as psoriasis, or atopic eczema, 6) conditions related to cardiovascular disorders such as angina, myocardial ischemia, hypertension, or platelet aggregation 7) renal insufficiency arising from ischaemia induced by immunological or chemical (cyclosporin) etiology, 8) migraine or cluster headache, 9) ocular conditions such as uveitis, 10) hepatitis resulting from chemical, immunological or infectious stimuli, 11) trauma or shock states such as burn injuries, or endotoxemia, 12) allograft rejection, 13) chronic lung diseases such as cystic fibrosis, bronchitis and other small and large-airway diseases, 4) cholecystitis, or 15) glomerular nephritis.

38. The use of a compound according to any one of claims 1 to 3, for prevention of side effects associated with therapeutic administration of cytokines such as interleukin II and tumor necrosis factor.

39. The use of a compound of any one of claims 1 to 3, for preparing a medicament for treating, preventing or ameliorating erosive gastritis; erosive esophagitis; diarrhea; cerebral spasm; premature labor; spontaneous abortion, dysmenorrhea; ischemia, noxious agent-induced damage of necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatotoxic agents; ischaemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; or glycerol-induced renal failure.

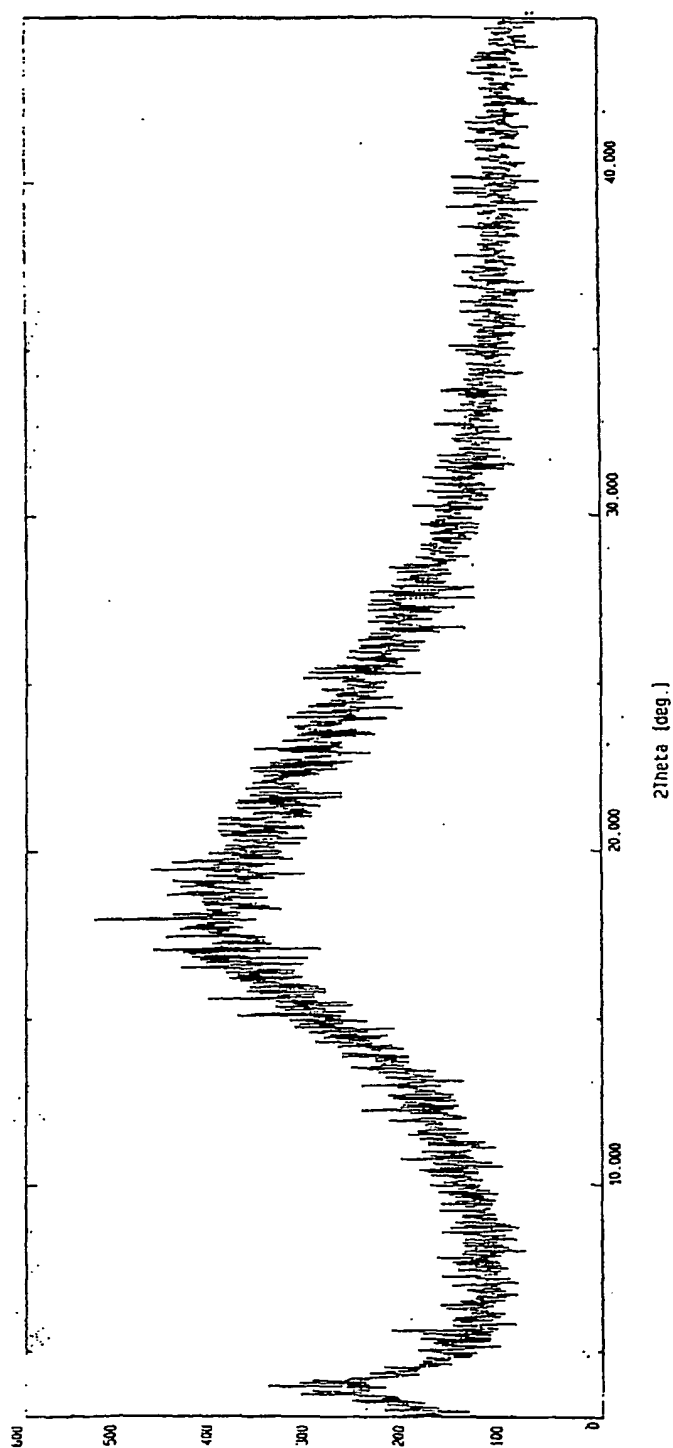


Fig. (1)

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D215/18 A61K31/47 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	---	3-31
A	WO 95 18107 A (MERCK & CO INC ;BHUPATHY MAHADEVAN (US); MCNAMARA JAMES M (US); SI) 6 July 1995 (1995-07-06) examples 8,14 -----	1-39

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

2 May 2003

Date of mailing of the international search report

09/05/2003

Name and mailing address of the ISA

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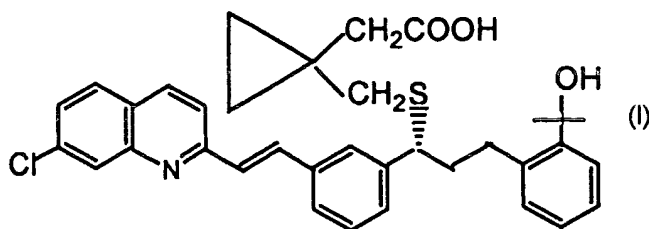
(19) World Intellectual Property Organization  
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(10) International Publication Number  
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- (51) International Patent Classification<sup>7</sup>: **C07D 215/18**, A61K 31/47, A61P 11/06
- (21) International Application Number: PCT/US03/03700
- (22) International Filing Date: 7 February 2003 (07.02.2003)
- (25) Filing Language: English
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- (30) Priority Data:  
94/MAS/2002 7 February 2002 (07.02.2002) IN
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- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**  
— with international search report
- (48) Date of publication of this corrected version:  
4 December 2003
- (15) Information about Correction:  
see PCT Gazette No. 49/2003 of 4 December 2003, Section II
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL ANHYDROUS AMORPHOUS FORMS OF MONTELUKAST SODIUM SALT



by the formula (I).

(57) Abstract: The present invention relates to novel anhydrous amorphous forms of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinoliny] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts (Montelukast alkali salts) to processes for their preparation, to compositions containing them and to methods of treatment using the same. Montelukast is a leukotriene antagonist, is useful as anti-asthmatic, anti-allergic, anti-inflammatory and cytoprotective agent. Montelukast is represented

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# PCT

REC'D 09 MAY 2003

## INTERNATIONAL SEARCH REPORT

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(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>94/MAS/2002</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. <b>PCT/US 03/ 03700</b>	International filing date (day/month/year) <b>07/02/2003</b>	(Earliest) Priority Date (day/month/year) <b>07/02/2002</b>
Applicant <b>DR. REDDY'S LABORATORIES LTD.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**NOVEL ANHYDROUS AMORPHOUS FORMS OF MONTELUKAST SODIUM SALT**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

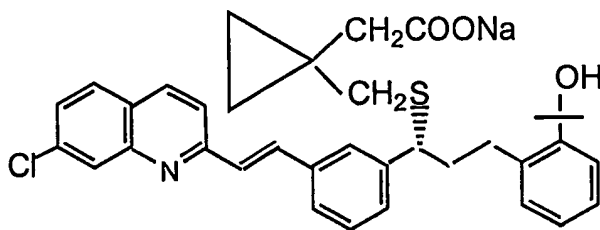
☒ None of the figures.

- 1 -

## NOVEL ANHYDROUS AMORPHOUS FORMS OF MONTELUKAST SODIUM SALT

The present invention relates to novel anhydrous amorphous forms of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts (Montelukast alkali salts) to processes for their preparation, to compositions containing them and to methods of treatment using the same.

Montelukast Sodium, chemically known as [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid (Montelukast) sodium salt is represented by the formula:



Montelukast sodium, a leukotriene antagonist, is useful as anti-asthmatic, anti-allergic, anti-inflammatory and cytoprotective agent and is hence useful in the treatment of angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis, and allograft rejection.

EP 480717 discloses certain substituted quinoline compounds including [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast sodium), and methods for their preparation.

The reported synthesis of Montelukast Sodium proceeds through corresponding methyl ester and involves coupling methyl 1-(mercaptomethyl) cyclopropaneacetate with a mesylate generated *in situ*. The methyl ester of Montelukast free acid is hydrolyzed to the free acid and the latter converted directly to the corresponding sodium salt. This process is not particularly suitable for large-scale production because it requires tedious chromatographic purification of the methyl ester intermediate and/or the final product, and the product yields are low.



- 2 -

WO Patent Application 95/18107 discloses an improved process for the preparation of crystalline Montelukast sodium salt, which comprises the generation of dilithium dianion of 1-(mercaptomethyl) cyclopropaneacetic acid followed by condensation with 2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl) ethenyl) phenyl)-3-methanesulfonyloxypropyl) phenyl)-2-propanol to afford the Montelukast acid which is then converted, via dicyclohexyl amine salt, to its corresponding sodium salt. The obtained sodium salt is further crystallized from a mixture of toluene: acetonitrile to obtain crystalline Montelukast sodium.

The PCT application further designates the products obtained as per EP 480717 as amorphous sodium salts, which are hydrated and often not ideal for pharmaceutical formulation.

It has been disclosed earlier that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to crystalline forms [Konne T., Chem pharm Bull., 38, 2003(1990)]. For some therapeutic indications one bioavailability pattern may be favoured over another. An amorphous form of Cefuroxime axetil is a good example for exhibiting higher bioavailability than the crystalline form.

Since Montelukast sodium is useful as anti-asthmatic, anti-allergic, anti-inflammatory and cytoprotective agent and amorphous forms of a number of drugs have been disclosed to exhibit different dissolution characteristics and in some cases different bioavailability patterns when compared to crystalline forms, the present invention, hence, aims to provide novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts and to processes for the preparation thereof.

The present invention also provides pharmaceutical compositions and pharmaceutical methods of treatment using novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts.

Another embodiment of the present invention is to provide methods for the preparation of the anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts (Montelukast alkali salts) which comprises dissolution of

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Montelukast free acid in aromatic hydrocarbon solvent or halogenated solvent and converting the free acid to its alkali salt, accompanied by addition of a cyclic or acyclic hydrocarbon solvent or mixtures thereof, followed by isolation of the desired compound.

Still another embodiment of the present invention is to provide pharmaceutical formulations containing an anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt.

An additional embodiment of the present invention is to provide pharmaceutical methods of treatment using anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts.

#### Brief Description Of The Accompanying Drawing

Fig. 1 is X-ray powder diffractogram of novel anhydrous amorphous form of Montelukast Sodium.

The present invention provides novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts, preferably, anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt.

The present invention also provides a process for preparation of anhydrous amorphous forms of Montelukast alkali metal salts. The anhydrous amorphous forms of Montelukast alkali metal salts are prepared by dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon. The solution of free acid of Montelukast is converted into alkali salt by use of alkaline metal hydroxide or an alkaline metal alkoxide in the presence of C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol or by use of alcoholic alkaline metal hydroxide or an alcoholic metal alkoxide.

One process for preparing amorphous forms of Montelukast alkali metal salts comprises:

- i) dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;

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- ii) converting the dissolved acid of step i) to corresponding alkali salt using an alkaline metal hydroxide or an alkaline metal alkoxide in the presence of C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol, followed by;
- iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent; and
- iv) isolating amorphous form of Montelukast alkali salt by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

According, to another embodiment, the present invention provides a process for preparation of amorphous forms of Montelukast alkali metal salts, which comprises:

- i) dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;
- ii) converting the dissolved acid of step i) to corresponding alkali salt using an alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide, followed by;
- iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent; and
- iv) isolating amorphous form of Montelukast alkali salt by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

The alkaline metal may be selected from calcium, sodium, potassium, or magnesium. Preferably, the alkaline metal is sodium.

According, to another embodiment, the present invention provides a process for preparation of novel anhydrous amorphous form of Montelukast Sodium, which comprises:

- i) dissolving the free acid of Montelukast sodium in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;
- ii) converting the dissolved acid of step i) to corresponding sodium salt using sodium hydroxide or sodium alkoxide in presence of C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol, followed by;
- iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent, and

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iv) isolating anhydrous amorphous form of Montelukast alkali salt sodium by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

According, to another embodiment, the present invention provides a process for preparation of novel anhydrous amorphous form of Montelukast Sodium, which comprises:

- i) dissolving the free acid of Montelukast sodium in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;
- ii) converting the dissolved acid of step i) to corresponding sodium salt using alcoholic sodium hydroxide or alcoholic sodium alkoxide in presence of C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol, followed by;
- iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent, and
- iv) isolating anhydrous amorphous form of Montelukast alkali salt sodium by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

In a preferred embodiment of the invention, the ratio of Montelukast free acid to C<sub>1</sub>-C<sub>2</sub> halogenated solvent or C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent in step i) is 1:1.5 to 1:6 w/v.

In a preferred embodiment of the invention, the ratio of Montelukast acid to C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol is 1:2-3 w/v.

In a preferred embodiment of the invention, the molar ratio of Montelukast acid to alkali metal hydroxide or alkaline metal alkoxide is 1:0.98 – 1.02, preferably, 1:1. In a preferred embodiment of the invention, the ratio of Montelukast acid to alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:2-4 w/v wherein the ratio of Montelukast acid to alkaline metal in alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:0.98 – 1.02 w/v. In step iii), the ratio of the reaction mass to the solvent is 1:1.2 to 1:4 w/v.

In precipitation of Montelukast alkali salt in step iv) the ratio of C<sub>1</sub>-C<sub>2</sub> halogenated solvent or C<sub>7</sub>-C<sub>8</sub> aromatic solvent to the C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon is 1:5 to 1:13 v/v. The preferred ratio is 1:6.5 v/v. This ratio is based on the amount of the C<sub>1</sub>-C<sub>2</sub> halogenated solvent or C<sub>7</sub>-C<sub>8</sub> solvent added in step iii).

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The C<sub>1</sub>-C<sub>2</sub> halogenated solvent may be selected from chloroform, dichloromethane or dichloroethane, preferably dichloromethane. The C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent may be selected from toluene, ethyl benzene or xylene, preferably toluene.

The alkali used in step ii) may be selected from sodium hydroxide, sodium methoxide, sodium ethoxide, methanolic sodium hydroxide, ethanolic sodium hydroxide, methanolic sodium methoxide, ethanolic sodium methoxide, methanolic sodium ethoxide, ethanolic sodium ethoxide, calcium hydroxide, calcium methoxide, calcium ethoxide, methanolic calcium hydroxide, ethanolic calcium hydroxide, methanolic calcium methoxide, ethanolic calcium methoxide, methanolic calcium ethoxide, ethanolic calcium ethoxide, potassium hydroxide, potassium methoxide, potassium ethoxide, methanolic potassium hydroxide, ethanolic potassium hydroxide, methanolic potassium methoxide, ethanolic potassium methoxide, methanolic potassium ethoxide, ethanolic potassium ethoxide, magnesium hydroxide, magnesium methoxide, magnesium ethoxide, methanolic magnesium hydroxide, ethanolic magnesium hydroxide, methanolic magnesium methoxide, ethanolic magnesium methoxide, methanolic magnesium ethoxide, ethanolic magnesium ethoxide, preferably the alkali is sodium hydroxide.

The C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol may be selected from methanol, ethanol, propanol, butanol, 2-propanol or tertiary butanol, preferably methanol. The C<sub>5</sub>-C<sub>7</sub> acyclic solvent may be selected from pentane, hexane, n-hexane, n-heptane or n-octane, preferably hexane or n-heptane. The C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon solvent may be selected from cyclopentane, cyclohexane or cycloheptane, preferably cyclohexane.

Novel anhydrous amorphous forms of Montelukast alkali salts may be characterized by the X-Ray powder diffraction pattern. The present invention provides anhydrous amorphous form of Montelukast Sodium that is characterized by its X Ray powder diffraction, substantially in accordance with Figure 1. The X-Ray diffraction pattern of anhydrous amorphous form of Montelukast Sodium was measured on a Rigaku Dmax 2000 with Cu K alpha-1 ISOKV/34mA, Degrees scanned: 3-45 degrees. Scan speed 3 degree/min.

The compounds of this invention can be used to prevent the synthesis, the action or the release of SRS-A or leukotrienes.

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The ability of the compounds of the present invention to antagonize the actions of the leukotrienes makes them useful for preventing or reversing the symptoms induced by the leukotrienes in a mammal including a human subject. This antagonism of the actions of leukotrienes indicates that the compounds of this invention and pharmaceutical compositions thereof are useful to treat, prevent, or ameliorate in mammals and especially in humans: 1) pulmonary disorders including diseases such as asthma, chronic bronchitis, and related obstructive airway diseases, 2) allergies and allergic reactions such as allergic rhinitis, contact, allergic conjunctivitis, and the like, 3) inflammation such as arthritis or inflammatory bowel disease, 4) pain, 5) skin disorders such as psoriasis, atopic eczema, and the like, 6) conditions related to cardiovascular disorders such as angina, myocardial ischemia, hypertension, platelet aggregation and the like, 7) renal insufficiency arising from ischaemia induced by immunological or chemical (cyclosporin) etiology, 8) migraine or cluster headache, 9) ocular conditions including inflammatory diseases such as uveitis, 10) hepatitis resulting from chemical, immunological or infectious stimuli, 11) trauma or shock states such as burn injuries, endotoxemia and the like, 12) allograft rejection, 13) prevention of side effects associated with therapeutic administration of cytokines such as interleukin II and tumor necrosis factor, 14) chronic lung diseases such as cystic fibrosis, bronchitis and other small and large-airway diseases, 15) cholecystitis and 16) glomerular nephritis.

The compounds of the present invention may also be used to treat or prevent mammalian (especially, human) disease states such as erosive gastritis; erosive esophagitis; diarrhea; cerebral spasm; premature labor; spontaneous abortion, dysmenorrhea; ischemia, noxious agent-induced damage of necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatotoxic agents such as  $\text{CCl}_4$  and D-galactosamine; ischaemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced renal failure. The compounds also exhibit cytoprotective action. (See EP 0480717).

The magnitude of prophylactic or therapeutic dose of a compound of this invention will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of this invention and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range for anti-asthmatic, anti-allergic or anti-inflammatory use and generally, uses other

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than cytoprotection, lie within the range of from 0.001 mg to 100 mg per kg body weight of a mammal, preferably 0.01 mg to 10 mg per kg, and most preferably 0.1 to 1 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

The pharmaceutical compositions of the present invention comprise an anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt, as an active ingredient and may also contain a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, solvent, binder, stabilizer and the like and optionally other ingredients used in pharmaceutical formulations. The compositions may also comprise one or more additional therapeutic agents. The compositions of this invention include compositions suitable for oral, rectal, topical, parenteral, ocular, pulmonary, or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. The compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of the pharmacy.

Dosage forms include tablets, troches, dragees, powders, syrups, patches, liposomes, injections, dispersions, suspensions, solutions, capsules, creams, ointments and aerosols. Compositions which provide from 0.1 to 10.0 mg of the active ingredient are preferred.

In general, an effective amount means that amount of a compound of this invention that will elicit the biological or medical response that is being sought. Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary and nasal administration, any be employed.

The Montelukast free acid used for the preparation of the novel anhydrous amorphous forms of Montelukast alkali salts is prepared as per processes known in the prior art.

The following examples illustrate the invention but do not construe to limit the same.

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**EXAMPLES****Reference Example****Preparation of Montelukast free acid**

Montelukast dicyclohexylamine salt (250.0 g, 0.326 moles) is suspended in dichloromethane (2.5 lit.), followed by addition of water (1.25 lit.), acetic acid (28 ml, 0.489 moles). The mixture is stirred for 30 minutes at ambient temperature. The layers are separated and the aqueous layer extracted with dichloromethane (1 x 500ml and 1 x 125 ml). The combined organic layers are washed with water (4 x 1.25lit.) and the organic layer separated. The organic layer thus obtained is dried over anhydrous sodium sulfate. The reaction solution is decanted, solvent from the reaction solution distilled under vacuum at below 50°C to afford the Montelukast free acid as residual mass.

**Example 1**

Montelukast free acid (260 g.) is dissolved in toluene (500ml) and the solvent is completely distilled off under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (750ml) and 0.5M methanolic sodium hydroxide solution (665ml) added and the mixture stirred for 15-30 minutes. The solvent from the reaction mass is distilled off under reduced pressure at below 50°C, followed by addition of toluene (500 ml) and distilling off 10-30% (v/v) of the reaction volume under reduced pressure at below 50°C. The concentrated reaction solution is added to hexane (2.5lit.) under Nitrogen atmosphere for 15-30 minutes at ambient temperature and stirred for 1-2 hours. The desired isolated compound is filtered under Nitrogen atmosphere and washed with hexane (500 ml), further the compound is filtered under vacuum. The wet compound was dried under vacuum at 70-80°C for 6-7 hours to yield amorphous form of Montelukast sodium. (Weight: 188 g., 94.90%, HPLC purity: 99.40%).

**Example 2**

Montelukast free acid (approx 26 g) is dissolved in toluene (50ml) and the solvent is completely distilled off under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (75ml) and 0.5M methanolic sodium hydroxide solution (69 ml) is added and the mixture stirred for 15-30 minutes. The solvent from the reaction mass was distilled off under reduced pressure at below 50°C followed by addition of toluene (300 ml) and charcoal treatment. The solvent from the reaction solution is



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distilled off completely under reduced pressure at below 50°C. The residual mass is dissolved in toluene (40 ml) and solution added to n-heptane (250 ml) under Nitrogen atmosphere for 15-30 minutes at ambient temperature and stirred for 1-2 hours. The desired isolated compound is filtered under Nitrogen atmosphere and washed with n-heptane (50 ml), further the compound is filtered under vacuum and dried under vacuum at 70-80°C for 2-3 days to yield amorphous form of Montelukast sodium. (Weight: 18.0 g., 91.0%, HPLC purity: 99.40%)

### Example 3

Montelukast free acid (14 g.) is dissolved in toluene (20 ml) and distilled off the solvent completely under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (30ml) and 0.5M methanolic sodium hydroxide solution (27 ml) is added and reaction mass stirred for 15-30 minutes. The solvent from the reaction mass is distilled off under reduced pressure at below 50°C followed by addition of toluene (20 ml) and distilling the solvent to obtain 10-30% (v/v) of the reaction volume under reduced pressure at below 50°C. The concentrated reaction solution is added to cyclo hexane (100 ml.) under Nitrogen atmosphere for 15-30 minutes at ambient temperature and stirred for 1-2 hours. The desired isolated compound is filtered under Nitrogen atmosphere and washed with cyclo hexane (20 ml), further the compound is filtered under vacuum. The wet compound is dried under vacuum at 70-85°C for 2-3 days to yield amorphous form of Montelukast sodium. (Weight: 6.8 g., 85.0%, HPLC purity: 99.10%).

### Example 4

Montelukast free acid (0 g.) is dissolved in toluene (20ml) and the solvent is distilled off under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (30ml) and 0.5M methanolic sodium hydroxide solution (27 ml) is added and reaction mass is stirred for 15-30 minutes. The solvent is distilled off completely under reduced pressure at below 50°C.

To the residue, dichloro methane (15 ml) is added. The resulting solution is added to n-heptane (200 ml) under nitrogen atmosphere for 15-30 minutes at ambient temperature. The reaction mass is stirred for 1-2 hours. The compound thus obtained is filtered under nitrogen atmosphere and washed with n-heptane (40 ml). The wet compound

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was dried under vacuum at 70-80°C for 2-3 days to yield amorphous form of Montelukast sodium. (Weight: 6.3 g., 78.70%, HPLC purity: 99.10%).

Fig-1 is characteristic X-ray powder diffraction pattern of amorphous form of Montelukast Sodium Salt. Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

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**CLAIMS**

1. Novel anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt (Montelukast alkali salt).
2. Novel anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast Sodium).
3. The amorphous form according to claim 2, characterized by an X-ray powder diffraction pattern substantially in accordance with Fig-1.
4. A process for the preparation of anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt (Montelukast alkali salt), which comprises the steps of:
  - i) dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;
  - ii) converting the dissolved acid of step i) to corresponding alkali salt using an alkaline metal hydroxide or an alkaline metal alkoxide in presence of C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol, followed by;
  - iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent, and isolating novel amorphous form of Montelukast alkali salt by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.
5. A process for the preparation of anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt (Montelukast alkali salt), which comprises the steps of:
  - i) dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;
  - ii) converting the dissolved acid of step i) to corresponding alkali salt using an alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide, followed by;

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iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent, and

iv) isolating novel amorphous form of Montelukast alkali salt by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

6. A process for the preparation of anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast sodium salt), which comprises the steps of:

i) dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an sodium hydroxide or an sodium alkoxide in presence of C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent, and

iv) isolating novel amorphous form of Montelukast sodium salt by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

7. A process for preparation of novel amorphous form of Montelukast Sodium, which comprises the steps of:

i) dissolving the free acid of Montelukast in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to the corresponding sodium salt using alcoholic sodium hydroxide or alcoholic sodium alkoxide, followed by;

iii) optionally dissolving the reaction mass of step ii) in C<sub>1</sub>-C<sub>2</sub> halogenated solvent or in C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent, and

iv) isolating novel amorphous form of Montelukast sodium by adding a C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon.

8. The process according to claim 4 or 5 wherein the alkaline metal is sodium, calcium, magnesium or potassium.

9. The process according to claim 4, wherein the alkaline alkoxide is selected from sodium methoxide or sodium ethoxide.

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10. The process according to claim 6, wherein the sodium alkoxide is sodium methoxide or sodium ethoxide.
11. The process according to claim 4, wherein the alkaline hydroxide is sodium hydroxide.
12. The process according to any one of claims 4 to 7, wherein the ratio of the free acid of Montelukast to C<sub>1</sub>-C<sub>2</sub> halogenated solvent or C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent in step i) is 1:1.5 to 1:6 w/v.
13. The process according to claim 4 or 6, wherein the ratio of Montelukast to C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol is 1:2-3 w/v.
14. The process according to claim 4, wherein the molar ratio of Montelukast acid to alkaline metal hydroxide or alkaline metal alkoxide acid is 1:0.98 – 1.02.
15. The process according to claim 6, wherein the molar ratio of Montelukast acid to sodium hydroxide or sodium alkoxide is 1:0.98 – 1.02.
16. The process according to claim 5, wherein the molar ratio of Montelukast acid to alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:2-4 w/v.
17. The process according to claim 7, wherein the molar ratio of Montelukast acid to alcoholic sodium hydroxide or alcoholic sodium alkoxide is 1:2-4 w/v.
18. The process according to claim 5, wherein the molar ratio of Montelukast acid to alkali in alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:0.98 – 1.02 w/v.
19. The process according to claim 7, wherein the molar ratio of Montelukast acid to sodium in alcoholic sodium hydroxide or alcoholic sodium alkoxide is 1: 0.98 – 1.02 w/v.
20. The process according to any one of claims 4 to 7, wherein in step iii), the ratio of the reaction mass to the solvent is 1:1.2 to 1:4 w/v.
21. The process according to any one of claims 4 to 7, wherein in step iv) the ratio of C<sub>1</sub>-C<sub>2</sub> halogenated solvent or C<sub>7</sub>-C<sub>8</sub> aromatic solvent to the C<sub>5</sub>-C<sub>7</sub> acyclic or C<sub>5</sub>-C<sub>8</sub> cyclic hydrocarbon is 1:5 to 1:13 v/v.
22. The process according to any one of claims 4 to 7, wherein the C<sub>1</sub>-C<sub>2</sub> halogenated solvent is selected from chloroform, dichloromethane or dichloroethane.

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23. The process according to claim 21, wherein the halogenated solvent is dichloromethane.
24. The process according to any one of claims 4 to 7, wherein the C<sub>7</sub>-C<sub>8</sub> aromatic hydrocarbon solvent is selected from toluene, ethyl benzene or xylene.
25. The process according to claim 24, wherein the aromatic hydrocarbon solvent is toluene.
26. The process according to any one of claims 4 or 6, wherein the C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol is selected from methanol, ethanol, propanol, butanol, 2-propanol or tertiary butanol.
27. The process according to claim 26, wherein the C<sub>1</sub>-C<sub>4</sub> straight or branched chain alcohol is methanol.
28. The process according to any one of claims 4 to 7, wherein the C<sub>5</sub>-C<sub>7</sub> cyclic hydrocarbon solvent is selected from cyclopentane, cyclohexane or cycloheptane.
29. The process according to claim 27, wherein the cyclic hydrocarbon solvent is cyclohexane.
30. The process according to any one of claims 4 to 7, wherein the C<sub>5</sub>-C<sub>8</sub> acyclic hydrocarbon solvent is selected from pentane, hexane, n-hexane, n-heptane or n-octane.
31. The process according to claim 29, wherein the acyclic hydrocarbon solvent is hexane or n-heptane.
32. A composition comprising an effective amount of a compound of any one of claims 1-3 and a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, solvent, binder or stabilizer.
33. The composition according to claim 31, in the form of a tablet, troche, dragee, powder, syrup, patch, liposome, injection, dispersion, suspension, solutions, capsule, cream, ointment or aerosol.
34. The use of a compound of any one of claims 1-3, for the manufacture of a medicament, for preventing the synthesis, the action, or the release of SRS-A or leukotrienes.
35. The use of a compound of any one of claims 1-3, for the manufacture of a medicament for treating asthma.
36. The use of a compound of any one of claims 1-3, for the manufacture of a medicament for treating inflammatory diseases of the eye.

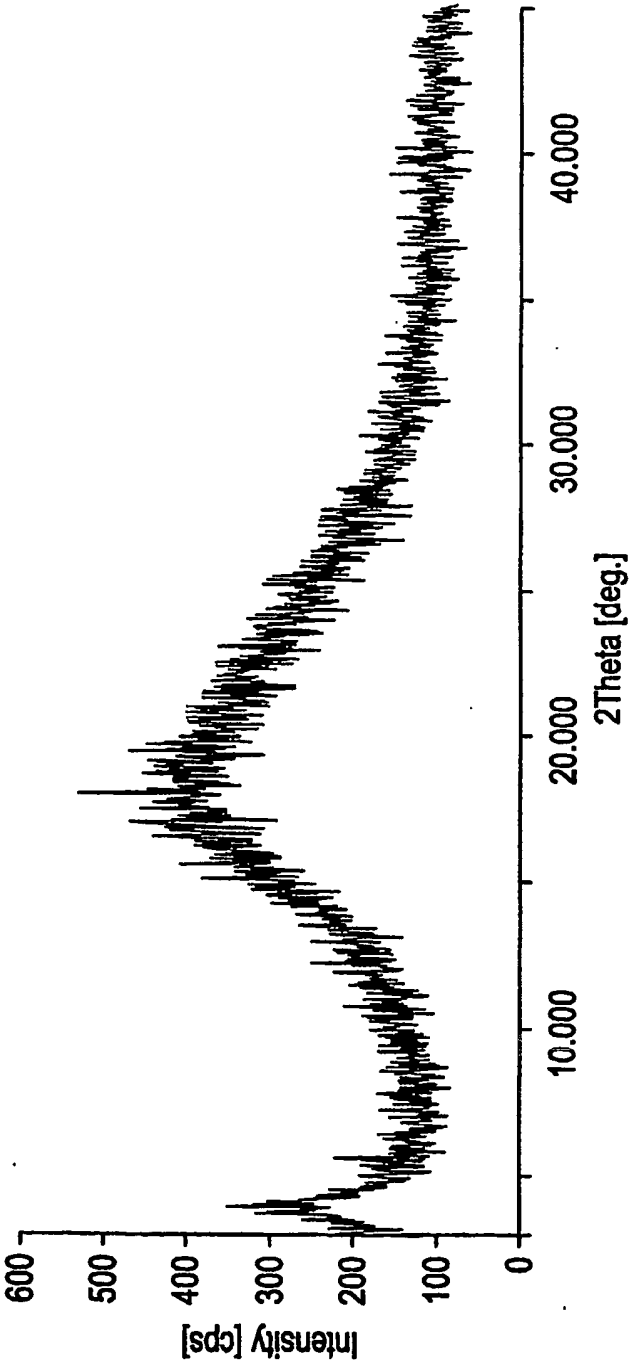
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37. The use of a compound of any one of claims 1 to 3, for preparing a medicament for treating, preventing or ameliorating 1) pulmonary disorders including diseases such as asthma, chronic bronchitis, and related obstructive airway diseases, 2) allergies or allergic reactions such as allergic rhinitis, contact dermatitis, or allergic conjunctivitis, 3) inflammation such as arthritis or inflammatory bowel disease, 4) pain, 5) skin disorders such as psoriasis, or atopic eczema, 6) conditions related to cardiovascular disorders such as angina, myocardial ischemia, hypertension, or platelet aggregation 7) renal insufficiency arising from ischaemia induced by immunological or chemical (cyclosporin) etiology, 8) migraine or cluster headache, 9) ocular conditions such as uveitis, 10) hepatitis resulting from chemical, immunological or infectious stimuli, 11) trauma or shock states such as burn injuries, or endotoxemia, 12) allograft rejection, 13) chronic lung diseases such as cystic fibrosis, bronchitis and other small and large-airway diseases, 4) cholecystitis, or 15) glomerular nephritis.

38. The use of a compound according to any one of claims 1 to 3, for prevention of side effects associated with therapeutic administration of cytokines such as interleukin II and tumor necrosis factor.

39. The use of a compound of any one of claims 1 to 3, for preparing a medicament for treating, preventing or ameliorating erosive gastritis; erosive esophagitis; diarrhea; cerebral spasm; premature labor; spontaneous abortion, dysmenorrhea, ischemia, noxious agent-induced damage or necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatotoxic agents; ischaemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; or glycerol-induced renal failure.

FIG. 1





## INTERNATIONAL SEARCH REPORT

National Application No

PCT/US 03/03700

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D215/18 A61K31/47 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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